REMARKS

Reconsideration of the present application is respectfully requested in view of the following remarks. Claims 43-49 and 51 are pending and under examination. Without acquiescence or prejudice, claim 51 has been amended. No new matter has been added by this amendment.

REJECTIONS UNDER 35 U.S.C. § 112, FOURTH PARAGRAPH

Claim 51 stands rejected under 35 U.S.C. § 112, fourth paragraph, for allegedly being of improper dependent form. It is asserted that claim 51 recites conditions associated with neuropathic cancer pain, and thus fails to further limit claim 43.

Applicants respectfully traverse this rejection. Nonetheless, the recitation "multiple myeloma" has been removed from the claims, and Applicants submit that the other conditions referred to by the Examiner are not necessarily cancer-associated conditions. For example, "alopecia" refers to loss of hair from the head or body, "ataxia-telangiectasia" is a neurodegenerative disease, and "vertebral ankylosing hyperostosis" is a skeletal condition characterized, for example, by ossification of spinal ligaments and tendon insertions.

Because the neuropathic pain associated with these conditions can be considered "non-cancer related neuropathic pain," as recited in claim 43, Applicants submit that claim 51 further limits claim 43, and satisfies the requirements of 35 U.S.C. § 112, fourth paragraph. Withdrawal of this rejection is therefore respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 103

A. Claims 43-45, 48-49, and 51 stand rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* (*Regional Anesthesia and Pain Medicine*. 18:4, 1993) in view of Williams *et al.* (U.S. Application No. 2004/0076648) and Chizh *et al.* (U.S. Application No. 2004/0092531). The Examiner agrees that Nickel *et al.* fail to teach the effect of flupirtine and an opioid on neuropathic pain, but asserts that Williams *et al.* and Chizh *et al.* remedy this deficiency, for example, by allegedly teaching the effect of ketamine and an opioid on

neuropathic pain (Chizh *et al.*), and by allegedly teaching that ketamine is predictive of flupirtine (Williams *et al.*).

B. Claim 46 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* in view of Williams *et al.* and Chizh *et al.*, as discussed above, and further in view of Perovic *et al.* (*Neurodegeneration.* 4:369-374, 1995). Perovic *et al.* are alleged to teach that flupirtine is a clinically safe compound that is non-sedating in most cases, from which the Examiner alleges that it would have been obvious to use flupirtine in combination with negligible amounts of morphine to avoid overt sedation.

Applicants respectfully traverse these rejections and submit that the instant claims satisfy the requirements of non-obviousness over the combination of cited references. Mainly, it is respectfully submitted that a *prima facie* case of obviousness has not been established for the use of flupirtine in combination with an opioid for treating non-cancer related neuropathic pain. Regardless, even assuming that the claimed combination has been shown to be *prima facie* obviousness, Applicants submit that its *unexpectedly* superior properties are sufficient to rebut any such showing.

The cited references fail to provide a reasonable expectation of success for methods of treating neuropathic pain. Instead, as recognized by the Examiner, Nickel *et al.* do not even mention *neuropathic* pain, and, as discussed on the record, provide no reason to expect the combination of flupirtine and an opioid to have any effect on *neuropathic* pain. Williams *et al.* do not help the Action's case, not only because they require the presence of an anti-depressant, and thus add one complicating factor, but also because they mischaracterize flupirtine as an NMDA receptor antagonist. As discussed below, Kornhuber *et al.* (*Journal of Neural Transmission*. 106:857-867, 1999) and others empirically show that flupirtine has no NMDA receptor antagonist activity at physiological relevant concentrations.

Chizh *et al.* then becomes essentially immaterial, because the only technical basis for the Action to extrapolate from the ketamine/opioid combinations of Chizh *et al.* to the flupirtine/opioid combinations of the instant claims is the allegedly shared NMDA receptor antagonist activity of ketamine and flupirtine. Because ketamine and flupirtine do not share this activity at physiologically relevant concentrations, and share no other activity of which

Applicants are aware, the cited references in combination fail to provide sufficient technical reason to combine flupirtine and an opioid for treating neuropathic pain. Applicants therefore submit that a *prima facie* case of obviousness has not been established.

Secondary Considerations of Non-Obviousness

Even assuming, *arguendo*, that a *prima facie* case of obviousness has been established, the patentability of the instant claims is strongly supported by secondary considerations of non-obviousness, which Applicants submit are sufficient to rebut any assumed *prima facie* case of obviousness.

Synergism as Evidence of Non-Obviousness. As here, synergism may point toward non-obviousness. *See* M.P.E.P. § 2141(I). As previously made of record, Applicants submit that the synergistic effects of the presently claimed subject matter are greater than expected from the art to an unobvious extent, provide significant practical advantages in the treatment of neuropathic pain, and are commensurate in scope with the claims. *See* M.P.E.P. § 716.02(a), citing *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991). It is also respectfully submitted that these synergistic effects would not have been expected from the combination of Nickels *et al.*, Williams *et al.*, and Chizh *et al.*

Applicants first submit that the instant facts differ from those of *In re Diamond and Kellman* (149 USPQ 562 (C.C.P.A. 1966), discussed at page 8 of Action. In that case, the Board agreed that the applicants would be entitled to prevail should they show unexpected synergism for the claimed combination (*See Id.* at 563); however, those applicants failed to show any relevant synergism.

Here, in contrast to *Diamond*, Applicants have shown that the combination of flupirtine and an opioid not only (i) creates positive synergy in treating neuropathic pain as claimed, but (ii) does so without magnifying the otherwise *shared* negative side-effects of these two drugs. As discussed extensively on the record, this combination synergistically enhances the analgesic activity of a given opioid dosage, without increasing sedation, a side-effect common to both agents. The treatments in Goodchild *et al.* (*Pain Medicine*. 9:939-949, 2008, previously submitted) further illustrate these beneficial effects in humans, by significantly improving overall

pain scores (*see* Table 3; ranging from about 20-54% improvement), but even more so, by *substantially* and therefore *selectively* improving *neuropathic pain* scores (*see* Table 4; ranging from 40-798% improvement with *most values far greater than 100%*). Because of the type of unexpected synergistic results unavailable in *Diamond*, it is believed that the Board in *Diamond* would have understood that Applicants here are entitled to prevail.

To that end, Applicants further submit that the synergistic and non-sedative properties of flupirtine in combination with an opioid are *unexpected*. The Federal Circuit as noted that in order to properly evaluate whether a superior property was unexpected, it should be considered what properties were expected. *Merck & Co. Inc. v. Biocraft Laboratories Inc.,* 874 F.2d 804, 808 (Fed. Cir. 1989). Here, Nickels *et al.* at best suggest an increase in analgesic activity for *nociceptive* pain. However, as discussed on the record, *nociceptive* pain fails to establish an expectation of synergy for *neuropathic* pain. Williams *et al.* are likewise deficient, partly because they require an anti-depressant to achieve their alleged effects, and merely suggest opioids as one possible add-on to their anti-depressant combination, among a laundry list of add-ons; they also mischaracterize flupirtine as an NMDA antagonist.

Chizh *et al.* at best create an expectation of synergistic results for the specific combination of ketamine (NMDA antagonist) and an opioid containing a fentanyl-type structure. However, ketamine (or any NMDA antagonist) would not have been considered predictive of flupirtine for this purpose. Despite Williams *et al.*, persons skilled in the art would have *not* considered flupirtine to be an NMDA antagonist. Instead, as detailed below, such persons would have understood from Kornhuber *et al.* (*Journal of Neural Transmission*. 106:857-867, 1999, submitted herewith) and others that the primary target of flupirtine is the GIRK channel, with flupirtine being the first modulator of this channel to be shown to have analgesic properties and therefore a "first in class" molecule. It is noted that Kornhuber *et al.*, at the Department of Psychiatry, University of Gottingen, were considered to be the leading experts on the NMDA receptor prior to the time of filing.

In explanation, NMDA receptor antagonists were known to be categorized pharmaceutically into four major groups according to the site of action on the receptor complex:

(1) NMDA recognition site;

(2) glycine (co-agonist) site;

(3) channel pore; and

(4) modulatory sites, such as the redox modulatory site, the proton-sensitive site, the high-affinity Zn^{2+} site, and the polyamine site.

Functional inhibition of NMDA receptors can be achieved through actions at different recognition sites through direct inhibition at the primary site, or allosterically at glycineB, polyamine, or phencyclicidine sites on the NMDA receptor complex itself. Kornhuber *et al.*, however, report that flupirtine does not have any of these characteristics, and, therefore, does not fall within the definition of an NMDA receptor antagonist.

On the basis of their review and analysis, Kornhuber *et al.* were of the opinion that flupirtine's physiological effects at plasma concentrations in the low micromolar range (at which it has analgesic activity) could be explained in terms of flupirtine acting to stabilize the resting membrane potential (*i.e.,* oppose excitation) by activating inwardly rectifying potassium channels. The prospect that flupirtine exerts a *direct effect* on NMDA receptors at physiologically-meaningful concentrations was dismissed by the authors. Neither the exact potassium current activated by flupirtine nor the channel configuration that mediates this current was identified by the authors. The authors, however, did state that flupirtine may *indirectly* affect the action of NMDA receptors, this indirect effect being a result of the Mg^{2+} block of the NMDA receptor remaining in force due to stabilization of the resting membrane potential (*see, e.g.,* page 864 of Kornhuber *et al.*). However, such an indirect effect can be ascribed to many other drugs as well, including the GABA antagonists such as baclofen and GABA analogues such as pregabalin and gabapentin, as well as many anticonvulsant drugs.

Thus, before the priority date of the instant application, specific research into the mechanism of action of flupirtine demonstrated that it activates an inwardly-rectifying potassium current in cultured hippocampal neurons and also demonstrated the *absence of a **direct effect** of flupirtine (at physiological meaningful concentrations) on NMDA receptors* in these neurons.

That there is a similarity between the effects of flupirtine and some NMDA receptor antagonists at the *behavioral* level has caused some understandable confusion with respect to the effect of flupirtine on analgesia. This is further complicated by the unfortunate use

of the term "functional antagonism" in relation to a drugs action on one target which may indirectly affect another target through membrane excitability. The fact that flupirtine is able to indirectly stabilize the resting potential by activating GIRK channel and thereby cause Mg^{2+} to remain blocking the NMDA receptor does not make flupirtine an NMDA receptor antagonist in any sense, or cause it to have the properties of the numerous NMDA receptor antagonists that now exist.

In relation to the finding that flupirtine may act as an indirect (*i.e.,* non-selective) NMDA receptor antagonist, Applicants note that prior to the study by Kornhuber *et al.*, independent studies into the mechanism of action of flupirtine were carried out using methods which were inappropriate for investigating the direct mechanism of action of flupirtine. For example, using the results of behavioral or neurotoxicity studies. It is widely recognized in the art that in order appropriately test the mechanism of action of a drug on ion channels, it is necessary to use a direct test, such as the whole cell patch clamp test. Here, Kornhuber *et al.* carefully analyzed the mechanism of action of flupirtine using direct whole cell patch clamp studies (*see, e.g.,* page 858; and pages 862-863), and found no direct effects on the NMDA receptor.

Kornhuber *et al.* further discuss the previous studies of Jakob and Krieglstein (*British Journal of Pharmacology*. 122:1333-1338, 1997, submitted herewith). These studies found "an activation of G-protein-regulated inwardly rectifying K+ channels by flupirtine in therapeutically relevant concentration ranges. According to our current knowledge, this is the only mechanism known to be relevant in a therapeutic concentration range." Jakob and Krieglstein investigated whether flupirtine is able to modulate potassium or NMDA-induced currents in rat cultured hippocampal neurons by use of the whole-cell configuration of the patch-clamp technique (*see* page 1333), and concluded that "the NMDA-induced currents <u>*were not reduced*</u> by this drug in cultured hippocampal nuerones or cortical neurons of the rat" (*see* page 1336) (emphasis added). Hence, Jakob and Krieglstein also empirically showed that flupirtine has no direct effect on the NMDA receptor.

In light of the above, it would have been clear to persons skilled in the art that Kornhuber *et al.* and others established, with compelling evidence, that flupirtine's mechanism

of action is not as an NMDA receptor antagonist. The previous assumption to that end (and possibly the later assumption of Williams *et al.*) had been made *without* supporting pharmacological evidence. For instance, Osborne *et al.* (1998) conducted a series of binding studies but could find no evidence to support that flupirtine had affinity for any of the well characterized binding sites associated with the NMDA receptor (*see* page 1336, second to last paragraph of Jakob and Krieglstein). Osborne *et al.* then *speculated* that flupirtine's action might be *via* the redox site in the NMDA receptor; however, this speculation was never supported experimentally. Kornhuber *et al.*, through actual patch clamp and binding experiments, confirmed that *flupirtine does not bind directly or at any of the allosteric sites on the NMDA receptor at therapeutically relevant concentrations*.

Further, Kornhuber *et al.* demonstrated that the concentrations of flupirtine required to exert an indirect effect on the NMDA receptor, which would equal the effect of a direct NMDA receptor antagonist, far exceeded the amount which would be achieved in clinical practice (*see* page 857 – "[o]nly very high concentrations of flupirtine antagonized inward currents to NMDA"). Kornhuber *et al.* therefore suggested that the use of flupirtine as an NMDA receptor antagonist had little relevance in a clinical sense (*see* pages 861-862 – "the therapeutically relevant concentrations of flupirtine are of *decisive importance* for assessing its molecular mechanisms of action…experimentally determined effects are only clinically relevant if they occur in the low micromolar range) (emphasis added). Thus, even flupirtine's potential *indirect effects* on NMDA receptors would have been considered of little or no clinical relevance.

This understanding of flupirtine's mechanism of action carries through to later days, even after the mischaracterization Williams *et al.* For instance, more recent reviews of clinically tolerated NMDA antagonists don't even mention flupirtine, even though flupirtine is well-known to be clinically tolerated (*see, e.g.,* Chen and Lipton, *Journal of Neurochemistry*. 97:1611-1626, 2006; and Childers and Baudy, *J. Mec. Chem*. 50:2557-2562, 2007, submitted herewith). Even assuming any lingering doubts as to the NMDA receptor-related activity of flupirtine, Childers and Baudy also illustrate the difficulties of extrapolating from one class of NMDA receptor antagonist to another (*e.g.,* from ketamine, a non-competitive NMDA receptor

antagonist at the PCP site, to an entirely different class of NMDA receptor antagonist), specifically in combination with opiates (*see* pages 2560-2561, carryover paragraph – where some NMDA receptor antagonists appear to work well with opiates and others do not).

Overall, in view of the empirical data on flupirtine's mechanism of action, showing that it has no direct or indirect NMDA receptor antagonist activity at clinically relevant concentrations, persons skilled in the art would have had no technical basis to extrapolate from the ketamine/opioid combination of Chizh *et al.* to the flupirtine/opioid combination of the instant claims. Applicants submit that the alleged synergism shown for ketamine/opioids is not predictive of the synergism shown for flupirtine/opioids, and that the synergistic effects described by Applicants were therefore entirely unexpected.

There is also no technical or mechanistic reason to expect these synergistic analgesic effects *in the absence of overt sedation*. Rather, as previously discussed, common technical sense suggests that when combining two agents with shared side-effects, such as sedation, somnolescence, nausea, hallucinations, etc., persons skilled in the art would have most reasonably expected the magnification of these shared side-effects (*see, e.g.,* Cleary, *Cancer Control*, of record). For example, even though adjuvant/opioid therapy has been recommended for pain, Cleary teaches that in his real-life experience of adjuvant therapy, "many patients...do not tolerate these medicines well and in fact *experience increased side effects*" (*see* page 127, column 2, last full sentence of Cleary) (emphasis added). As another example, Dionne achieved an additive increase in the analgesic effects of ibuprofen and opioids, *but at the expense of an increased incidence of adverse events* (*see* Dionne, *Journal of Oral and Faciomaxillary Surgery.* 57:673-678, 1999, abstract previously submitted). As a third example, de Craen *et al.* (*BMJ.* 313:321–325, 1996, previously submitted) found that multi-doses of a combination of paracetamol/codeine caused a significantly higher proportion of side effects compared to each agent alone. Hence, as noted above, persons skilled in the art understood the difficulties in identifying effective analgesic combinations that do not have magnified, dose-related side effects, and would have set their expectations accordingly – well below the synergism described for the presently claimed combination.

Applicants have described at least two *unexpected* and *superior* properties for the claimed combination of flupirtine and an opioid, specifically for treating *neuropathic* pain, as claimed. First, flupirtine synergistically enhances the analgesic activity of opioids in reducing neuropathic pain, and second, it does so without magnifying the dose-related sedative effects of these two agents. For neuropathic pain, Applicants therefore submit that synergistic results provided by the presently claimed combination are greater than those that would have been expected from the cited art to an unobvious extent.

Applicants therefore submit that the instant claims satisfy the requirements of non-obviousness over the combination of cited references, and respectfully request withdrawal of the rejections under 35 U.S.C. §103(a).

Applicants believe that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

/William T. Christiansen/
William T. Christiansen, Ph.D.
Registration No. 44,614

WTC:MER:jto

Enclosures:

Kornhuber *et al.*, *Journal of Neural Transmission*. 106:857-867, 1999
Jakob and Krieglstein, *British Journal of Pharmacology*. 122:1333-1338, 1997
Chen and Lipton, *Journal of Neurochemistry*. 97:1611-1626, 2006
Childers and Baudy, *J. Mec. Chem*. 50:2557-2562, 2007

701 Fifth Avenue, Suite 5400
Seattle, Washington 98104
Phone: (206) 622-4900
Fax: (206) 682-6031

1850335_1.DOCX